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Osteoporosis, identification and treatment in fracture patients

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Chapter 9

Summary and conclusions

In this thesis different aspects of osteoporosis screening in patients with a fracture are described in order to improve the screening. Osteoporosis is a systemic disease of the bones characterized by a low bone mineral density (BMD) *and/or* a reduced bone quality, resulting in an increased fracture risk. BMD is defined as the peak bone mass (reached around the age of thirty) minus the rate of bone loss in the years thereafter. Because of the proportionally increase of the ageing population, the number of osteoporotic patients will increase in the next few years. The sensitivity of diagnosing osteoporosis is low, which implies that a general screening program for osteoporosis should not be recommended. However, it is worthwhile to screen patients at high risk so as to prevent subsequent fractures. Patients older than 50 with a fracture are an important group of patients who are at high risk for osteoporosis. Fractures of the hip, vertebra, humerus, ankle and wrist are typical osteoporotic fractures. Hip fractures and vertebral fractures have the largest impact, as they result in excess mortality and serious disability.

The golden standard for diagnosing osteoporosis is the measurement of BMD with Dual Energy X-ray Absorptiometry (DXA) of the hip and/or spine. For each decrease in BMD by 1SD, the fracture risk is doubled. Patients with a $BMD \leq -2.5SD$ are considered to be osteoporotic. The treatment of these patients will decrease the subsequent fracture risk up to 50%. But, DXA has some disadvantages: BMD is underestimated in small bones and overestimated in large bones, as well as in patients with degenerative changes and obese patients. Moreover, most clinics do not always have DXA available immediately, which is another disadvantage. This is an important issue because most subsequent fractures occur in the first year after the initial fracture and the time to benefit (TTB) from osteoporotic medication is, concerning the most recent literature, up to 11 months. It is therefore important to initiate anti-osteoporotic therapy as soon as possible. There are other techniques to predict fracture risk. One of these techniques is the Calscan, a peripheral Dual Energy X-ray Absorptiometry device. The Calscan measures BMD at the calcaneus and adds a laser beam to conventional DXA technique, which makes it possible to measure BMD without the influence of adipose tissue. The Calscan has many advantages. It is a portable device and easy in use. Moreover, measurements take less time than DXA, the effective radiation dose is low ($<0.2\mu Sv$), and even immobile patients or patients with problems in positioning the hip can be scanned. If the Calscan proves to be a valid measurement device it might be used to increase the percentage of patients being screened for osteoporosis, which is of great importance as this percentage is at present still too low.

From a historic point of view, the organization of osteoporosis screening through a Fracture Liaison Service (FLS) was a big improvement in increasing the percentage of patients being screened for osteoporosis. The first FLS was implemented in 1999 in Glasgow, Scotland. An FLS includes the following 5 basic elements: case-finding, risk assessment, medical history + clinical examination + laboratory tests, treatment decision, and follow up. In 2003 the first Dutch FLS was set up at the University Medical Center Groningen, soon followed by other hospitals. In the Netherlands the FLS also proved to be a good instrument to increase the percentage of patients being screened for osteoporosis (from 5 to 51%). Furthermore, it resulted in a high compliance with anti-osteoporotic drug treatment (up to 88% after 1-year treatment), and the rate of subsequent fractures

decreased (2% after 1 year, instead of 6.5% as previously described). On the other hand, 50% of the patients are not attending the FLS. A reason frequently mentioned by patients is that they think they are too old to visit the FLS and that treatment would not be useful anymore. However, it is this elderly group of (often disabled) patients that would probably benefit most from fracture prevention. It therefore remains challenging to further optimize the screening for osteoporosis. The aim of this thesis is to describe options which can further improve the screening for osteoporosis, including the use of the Calscan.

A vertebral fracture can be seen as a proof for osteoporosis, independent of BMD. Therefore measurement of BMD in patients with a vertebral fracture is not strictly necessary. In **chapter 2** of this thesis we established the prevalence of vertebral fractures in patients screened at our FLS. This study described 176 patients admitted to the FLS. At the FLS spinal radiographs were obtained and BMD was measured by DXA. The prevalence of vertebral fractures in our study population was 42%. Of all vertebral fractures only 18% were symptomatic. Spinal imaging is therefore important to diagnose vertebral fractures. Osteoporosis (defined as a vertebral fracture and/or an osteoporotic BMD) was diagnosed in 54% of all patients. It was possible to identify 77% of osteoporotic patients because they suffered from a vertebral fracture. Another important result from this study was that 64% of all patients with a vertebral fracture did **not** suffer from an osteoporotic BMD. Therefore, conform the Dutch consensus on "Osteoporosis and Fracture Prevention", a vertebral fracture should be considered as proof for osteoporosis in order not to deny patients adequate anti-osteoporotic treatment. Whenever possible, the combination of BMD measurement and assessment of the spinal column is the best way in screening for osteoporosis at an FLS. In this regard it is interesting to realize that nowadays software is available for most DXA machines to provide images from the thoracic and lumbar vertebrae. This offers the possibility of BMD measurement combined with morphometry or vertebral fracture assessment (VFA). In case DXA is not available, spinal radiographs can be used as a first step in screening for osteoporosis.

Osteoporosis in patients with a distal radial fracture is related to malunion, early instability and late carpal malalignment. Early information about the osteoporotic status of a patient with a distal radial fracture could thus be helpful in choosing an operative or conservative approach. In **chapter 3** we described the relation between the AO-fracture classification of distal radial fractures and BMD, to conclude whether or not the AO-classification could be used as a screening for osteoporosis. Furthermore, the prevalence of subsequent fragility fractures was calculated and the time interval between the initial and subsequent fragility fracture. This study described 208 patients. BMD was measured at the left hip and lumbar spine by DXA in a standardized fashion. All distal radial fractures were confirmed on the radiograph at the time of admission and classified according to the AO classification system by a trauma surgeon. Subsequent fragility fractures were recorded from the hospital registration system. In 176 (85%) patients the follow up was at least 1 year. There was no correlation between the AO-fracture classification system and BMD. A subsequent fragility fracture occurred in 5.3% of patients, significantly more often in osteoporotic patients. The median time interval after which a subsequent fracture occurred was 138 days, which was close to the median time interval after which osteoporosis screening was performed, being 83 days. This is an important result because

the time to benefit (TTB) from osteoporotic medication is at least 90 days. We concluded that the AO-classification system of distal radial fractures is not useful in screening for osteoporosis. Though we consider early screening for osteoporosis in patients with distal radius fractures of importance because the median time interval of subsequent fractures is only 138 days and osteoporotic patients might benefit from early operative treatment to prevent malunion. In our series only 8.8% of osteoporotic patients with a distal radial fracture were treated operatively.

In **chapter 4** we compared the BMD measured by DXA and Calscan in 182 patients over 50 years of age. The mean age was 66 years. The aim of this study was to define threshold T-scores on the Calscan that could exclude or predict osteoporosis correctly in comparison with DXA. These thresholds are defined in a way that patients with osteoporosis of the hip or spine are identified with 90% sensitivity and 90% specificity. The upper threshold for the Calscan is therefore the Calscan T-score under which 90% of patients with osteoporosis are classified by the Calscan as having osteoporosis (sensitivity). All patients with a Calscan T-score above the upper threshold are considered not to suffer from osteoporosis. The lower threshold for the Calscan is the Calscan T-score above which 90% of the patients without osteoporosis were classified by the Calscan as not having osteoporosis (specificity). All patients with a Calscan T-score under or equal to the lower threshold were considered to suffer from osteoporosis. Patients in between both thresholds could not be classified by the Calscan. With an upper threshold on the Calscan T-score of -1.4SD, 91.1% of the osteoporotic patients were classified correctly by the Calscan. Using a lower threshold on the Calscan T-score of -2.9SD, 90.5% of non-osteoporotic patients were correctly classified by the Calscan. When both thresholds were used 28.6% of the patients did not have to be assessed by DXA because of the low probability of osteoporosis and 18.7% did not need DXA evaluation because of the high probability of osteoporosis. Therefore, 47% of the patients could be reliably classified on the basis of the Calscan T-score and did not need further DXA evaluation. In **chapter 5** we validated the Calscan in screening for osteoporosis in patients ≥ 65 years with a hip fracture, in the same manner as described in chapter 4. For this study 108 patients were included, with a mean age of 78 years. With an upper threshold on the Calscan T-score of -1.8SD, 91.4% of the osteoporotic patients were classified correctly by the Calscan. Using a lower threshold on the Calscan T-score of -3.5SD, 89% of non-osteoporotic patients were correctly classified by the Calscan. When both thresholds were used 30% of the patients did not have to be assessed by DXA because of the low probability of osteoporosis and 23% did not need DXA evaluation because of the high probability of osteoporosis. Therefore, 53% of the patients could be reliably classified on the basis of the Calscan T-score and did not need further DXA evaluation. From these two studies we concluded that the Calscan was a valid measurement instrument which can be used as a first step in screening for osteoporosis. It also became clear that with increasing age, thresholds on the Calscan T-score decrease. Another important result from the study presented in chapter 5 was that only 44% of hip fracture patients over 65 years had been screened for osteoporosis.

In **chapter 6** we evaluated whether the percentage of patients that can be classified and treated will increase when the Calscan is used in the screening for osteoporosis. Furthermore, the study was designed to provide more insight into why and which patients opt out of a screening for osteoporosis at the FLS. A Calscan was performed in all patients during admission to the hospital. Bisphosphonates were clinically administered to patients who were classified osteoporotic based on their Calscan T-scores. Because, in the Netherlands, a BMD measurement with a DXA scan is still the golden standard, all patients were also referred to the FLS to undergo a DXA scan. The final treatment plan was drawn up based on the results of this DXA scan. A DXA T-score $\leq -2.5SD$ is used in this study to proof osteoporosis. The results of earlier studies – in which the cut-off points for the Calscan were determined – were used in order to diagnose osteoporosis with the Calscan. Because the American guideline on Osteoporosis classifies hip-fracture patients as being osteoporotic, without a previous BMD measurement, we presented the results of our study for the general group of fracture patients and the group of non-hip fracture patients. We described 164 patients, of which 105 (64%) were actually screened through our FLS. Of the 59 patients who did not show up at our FLS, 14 patients could be classified as non-osteoporotic by the Calscan and 17 patients were classified osteoporotic by the Calscan. This means that, with the use of the Calscan in the screening for osteoporosis, the percentage of patients that can be classified can increase from 64 to 83%. Of all 164 patients, 78 suffered from a hip fracture. Of the 86 non-hip fracture patients, 62 (72%) attended the FLS. Of the 24 patients who did not show up at the FLS, 2 patients could be classified normal and 8 osteoporotic, based on the Calscan T-scores. This means that, if the Calscan had been used in the screening for osteoporosis among patients with a non-hip fracture, 84% could have been reliably classified. If, in the analysis of the entire group of fracture patients, a hip fracture is seen as proof for osteoporosis, and non-hip fracture patients are classified based on their DXA scan and in case no DXA scan is available the Calscan, 91% of all patients could be classified. This study also demonstrated that those who didn't show up at the FLS were significantly older compared to those patients who showed up. Moreover, patients who were admitted from a nursing home or discharged to a nursing home or those who are cognitively impaired, opt out of further studies into osteoporosis significantly more often, even though this group often includes the vulnerable elderly people with an increased risk of falling. Furthermore this study showed that 47% of the patients with a hip fracture were not screened for osteoporosis at the FLS, while a hip fracture can be seen as proof for osteoporosis. Our conclusion is that the Calscan can be a valuable addition to the screening for osteoporosis, particularly because the Dutch 'Osteoporosis and Fracture Prevention' guideline cannot be properly implemented using only DXA. The Calscan can be performed during the patient's admission, which will also increase the percentage of vulnerable elderly patients who are screened for osteoporosis. Additionally, it would be wise to treat every elderly patient with a hip fracture for osteoporosis until its existence can be ruled out with a DXA scan.

In **chapter 7** we focused on the value of a standard set of laboratory tests to screen for secondary osteoporosis at the FLS. Secondary osteoporosis was defined as an underlying disease resulting in a decreased BMD. The study population comprised 499 patients. Our standard set of laboratory tests included: hemoglobin, hematocrit, mean corpuscular volume, creatinine, glucose, thyroid stimulating hormone, free thyroid

hormone, phosphorus, calcium, gamma glutamyl transpherasis, and alkaline phosphatase. Laboratory results were as often abnormal in patients with a normal BMD compared to patients with a low BMD. For the purpose of this study, we considered laboratory testing useful when the prevalence of underlying diseases was at least 15%. This was only true for osteoporotic male patients in which the prevalence was up to 18.2%. We concluded that it is probably not useful to screen all patients at an FLS on underlying diseases by obtaining a standard set of laboratory tests, but male osteoporotic patients might benefit from this screening.

General conclusions and recommendations are addressed in **chapter 8**. This thesis focused on improving the screening for osteoporosis in fracture patients. It is important to realize that osteoporosis is defined as a low BMD **and/or** a diminished bone quality. We described that both vertebral fractures and hip fractures can represent proof for diminished bone quality and thus osteoporosis. This is an important conclusion because the prevalence of vertebral- and hip fractures is high. By including these fractures in the screening for osteoporosis the need for BMD measurement with a DXA scan will diminish and the number of patients being screened for osteoporosis will increase. Apart from vertebral- and hip fractures, it is known that distal radial fractures in elderly patients are associated with osteoporosis. However, we could not find a correlation between BMD and the AO classification for distal radial fractures. The AO classification can therefore not be used to exclude or prove osteoporosis. On the other hand, the Calscan proved to be a valid measurement device to measure BMD. Using the Calscan in the screening for osteoporosis can further improve the percentage of patients being screened. Adequate screening for osteoporosis also includes the screening for secondary osteoporosis. We found a relatively low percentage of secondary osteoporosis in our study and recommend to screen only male osteoporotic patients for secondary osteoporosis. However, recently some new insights in the definition and importance of screening for secondary osteoporosis were published. It was emphasized that secondary osteoporosis not only points to contributors decreasing BMD, but also affecting bone quality, or even both, resulting in an increased fracture risk. The term SECOB (secondary osteoporosis and other metabolic bone diseases) was introduced, which is more adequate than secondary osteoporosis, as SECOB can be found in patients with a recent clinical fracture, regardless of BMD. The prevalence of contributors to SECOB described in recent literature is - with 26-51% - higher than the prevalence of secondary osteoporosis we calculated in our study. The difference in prevalence of secondary osteoporosis found in our study and SECOB in other studies can be explained by the different definitions of osteoporosis and the different panel of laboratory tests used in the different studies. Despite the high prevalence of SECOB at an FLS, the true advantage of screening for contributors to SECOB has to be determined, because there is no evidence that this will reduce fracture risk. Moreover, a cost effectiveness analysis is lacking. These are the reasons that in my opinion it is still questionable whether or not a standard set of laboratory tests should be used at an FLS.